ATTACHMENT A
R marks

Claims 1-13, 15 and 16 are pending in the present application. By this Amendment, Applicants have amended claims 1-3. Applicants respectfully submit that the present application is in condition for allowance based on the discussion which follows.

The specification was objected to for including terms which were deemed vague including the terms "biologically active", "similar" and "metalloprotease activity". By this Amendment, Applicants have amended claims rendering the specification objection moot in that the claims no longer encompass biologically active fragments of the claimed polypeptide. Accordingly, Applicants respectfully request that the objection to the specification be withdrawn.

Claims 1-2, 4-6, 11 and 13, 15 and 16 were rejected under 35 U.S.C. § 101 for lacking patentable utility for the human NEP2. Applicants respectfully submit that the claimed human NEP2 polypeptide does provide for the enzymatic activity of the claimed polypeptide. By this Amendment, Applicants have submitted a Rule 132 Declaration by co-inventor Tanja Ouimet who supports the enzymatic activity of NEP2 by providing further experimental data demonstrating the enzymatic activity of the claimed polypeptide. More specifically, the experimental data demonstrates that human NEP2 has enzymatic activity characteristic of a metalloprotease and furthermore that human NEP2 is closely related to rat NEP2 and other polypeptides isolated by the inventors. Based on the foregoing, Applicants respectfully submit that the claimed invention does contain patentable utility and therefore Applicants respectfully request that the rejection to the claims under 35 U.S.C. § 101 be withdrawn.

Claims 1-2, 4-6, 11 and 13 were rejected under 35 U.S.C. § 112, second paragraph. In order to move this case forward to allowance and therefore without addressing the merits of the rejection, Applicants have amended the claims thereby rendering the 35 U.S.C. § 112, second paragraph rejection moot. Specifically, the claims and in particular claim 1 has been amended to be limited to a polypeptide comprising the amino acid sequence encoded by the nucleic acid of sequence SEQ ID NO: 3. Accordingly, Applicants respectfully request that the rejection to the claims under 35 U.S.C. § 112, second paragraph, be withdrawn.

Claims 1-2, 4-6, 11, 13 and 14-16 were rejected under 35 U.S.C. § 112, first paragraph for lacking adequate written description. With regard to the Examiner's opinion that the definition of polypeptide SEQ ID NO: 4 is unclear, and that there is a lack of unity between SEQ ID NO: 3 and SEQ ID NO: 4, Applicants respectfully traverse the Examiner's allegations. However, to accelerate prosecution of the present application, the polypeptide claim has been redrafted to refer to the sequence encoded by SEQ ID NO: 3 rather than to a polypeptide of SEQ ID NO: 4. Accordingly, Applicants respectfully submit that the rejection under 35 U.S.C. § 112, first paragraph, based on a lack of unity between SEQ ID NO: 3 and SEQ ID NO: 4 is now moot.

Further, with regard to the rejection based on a reference to a homologous or derived sequence, Applicants respectfully submit that the rejection to claims 1, 6, 11, 13 and 15-16 as well as claims 2, 4 and 5, is now moot as the reference to a homologous or derived sequence has now been canceled from the claims.

With regard to the rejection of claims 15 and 16 for reciting "the polypeptide transmission in which NEP2 participates" alleging that the specification fails to disclose

in which polypeptide transition human NEP2 is involved, Applicants respectfully submit that Example 4 in the present application indicates that NEP2 is involved in the metabolism of neuronal and/or hormonal messenger peptides.

Furthermore, this assertion is supported by the results provided by inventor Ouimet in her Declaration (provided herewith) wherein it is demonstrated that human NEP2, the claimed polypeptide, hydrolyses gonadotropin-releasing hormone (GnRH), a peptide released from the hypothalamus that is implicated in the regulation of reproduction in vertebrates (gonadal development), and met-enkephalin, an opioid peptide that participates in neurotransmission and neuromodulation in the nervous system. Consequently, Applicants respectfully submit that the specification as filed does support a conclusion that the Applicants had possession of the claimed invention at the time the present application was filed. Furthermore, the now confirmed human NEP2 activity was further demonstrated for rat NEP2 and published in the Rose et al (2002) article previously submitted with the Amendment on May 5, 2003. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection to claims 15 and 16 under 35 U.S.C. § 112, first paragraph.

Finally with regard to the rejection to the claims for including the term "comprise" as making the invention not commensurate in scope with the specification, Applicants respectfully submit that the claimed scope has been sufficiently limited by this Amendment via canceling reference to the homologous sequence and biological activity fragments. Thus, the present invention is now limited to an isolated polypeptide comprising an amino acid sequence encoded by the nucleic acid sequence of SEQ ID NO: 3. Since the claimed invention is sufficiently limited, Applicants respectfully submit

that the claims are fully supported by the specification as filed and therefore, Applicants respectfully request that the rejections to the claims under 35 U.S.C. § 112, first paragraph, be withdrawn.

Claim 6 was rejected under 35 U.S.C. § 102(b). The rejection to claim 6 is now moot since claim 6 no longer encompasses antibodies directed against polypeptides homologous to SEQ ID NO: 4. Accordingly, claim 6 is not anticipated by Ritz et al since Ritz et al teach production of an antibody against a sequence which is 66.7% identical to SEQ ID NO: 4. Therefore, Applicants respectfully request that the rejection to claim 6 be withdrawn.

Claim 3 was rejected under 35 U.S.C. § 102(b) as being anticipated by Bonaldo et al. However, the Examiner suggested that changing the claim to "An oligonucleotide probe consisting of a nucleotide sequence..." would avoid the Bonaldo et al reference which discloses nucleotide sequences comprising SEQ ID NOS: 15 and 20. By this Amendment, Applicants have adopted the Examiner's suggestion thereby overcoming the rejection based on Bonaldo et al.

In view of the foregoing, Applicants respectfully submit that the present application is in condition for immediate allowance.

END REMARKS

ATTACHMENT B
Am ndments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application.

1. (Currently Amended) An isolated polypeptide comprising an amino acid sequence ~~selected from the group consisting of the sequence SEQ ID NO: 2 or SEQ ID NO: 4, a sequence derived from or homologous to said sequence SEQ ID NO: 2 or SEQ ID NO: 4, said derived or homologous sequence having at least 75% sequence identity with SEQ ID NO: 2 or SEQ ID NO: 4, and a biologically active fragment of said sequence SEQ ID NO: 2 or SEQ ID NO: 4,~~ encoded by the nucleic acid sequence SEQ ID NO: 3, said isolated polypeptide being referred to as "NEP2".

2. (Currently Amended) An isolated nucleic acid comprising ~~a~~ the nucleotide sequence ~~selected from the group consisting of SEQ ID NO: 1 or~~ SEQ ID NO: 3, ~~a sequence derived from or homologous to said sequence SEQ ID NO: 1 or SEQ ID NO: 3 having at least 75% sequence identity thereof, and~~ or the complementary sequences thereof.

3. (Currently Amended) An oligonucleotide probe ~~having~~ consisting of a nucleotide sequence chosen from the sequences SEQ ID NO: 5 to SEQ ID NO: 27.

4. (Original) A cloning and/or expression vector containing a nucleotide sequence as claimed in claim 2.

5. (Original) A host cell transfected with a vector as claimed in claim 4.

6. (Previously Presented) Mono- or polyclonal isolated antibodies or their fragments, chimeric isolated antibodies or immunoconjugates, characterized in that they are obtained using a polypeptide as claimed in claim 1 administered to an animal, and are capable of recognizing specifically a polypeptide as claimed in claim 1.

7. (Withdrawn) A method for immunologically detecting NEP II in a cell or tissue sample or in cells or a tissue, comprising the steps consisting in:

- brining said cell or tissue sample, said cells or said tissue into contact with a detectable antibody as claimed in claim 6;
- detecting the presence of said antibody, which is an indication of the presence of the NEP II polypeptide.

8. (Withdrawn) A method for detecting the expression of the NEP II polypeptide in a cell or tissue sample or in cells or a tissue, by *in situ* hybridization, comprising the steps consisting in:

- preparing the RNA of said sample or of said cells or of said tissue;
- bringing said RNA obtained into contact with at least one probe having a nucleotide sequence which is capable of hybridizing specifically with a nucleotide sequence as claimed in claim 2, said probe possibly being in particular an oligonucleotide probe as claimed in claim 3;

- detecting the presence of mRNA hybridizing with said probe, which indicates the expression of the NEP II polypeptide.

9. (Withdrawn) A method for detecting the expression of the NEP II polypeptide in a cell or tissue sample or in cells or a tissue, by *in situ* hybridization, comprising the steps consisting in:

- preparing the RNA of said sample or of said cells or of said tissue;
- bringing said RNA obtained into contact with at least one probe having a nucleotide sequence which is capable of hybridizing specifically with a nucleotide sequence as claimed in claim 2; and
- detecting the presence of mRNA hybridizing with said probe, which indicates the expression of the NEP II polypeptide.

10. (Withdrawn) A method for detecting the metalloprotease activity of NEP II in a cell or tissue sample or in cells or a tissue, comprising the steps consisting in:

- bringing said cell or tissue sample, said cells or said tissue into contact with a compound which is a substrate for the NEP II polypeptide, obtained according to the method of claim 9, said substrate compound being optionally labeled;
- evaluating the cleavage of said substrate compound, which is an indication of the metalloprotease activity of NEP II.

11. (Previously Presented) A method for screening compounds which are capable of inhibiting the metalloprotease activity of the NEP2 polypeptide as claimed in claim 1; said method comprising the steps of:

measuring NEP2 activity in the presence or absence of a test compound, under conditions sufficient for NEP2 activity to be measured in the absence of a test compound, and

comparing NEP2 activity as measured in the presence of the test compound with that measured in the absence of the test compound,

wherein a decreased activity in the presence of the test compound is indicative of a compound capable of inhibiting the metalloprotease activity.

12. (Withdrawn) A method for detecting NEP II in a cell or tissue sample or in cells or a tissue, comprising the steps consisting in:

- bringing said cell or tissue sample, said cells or said tissue into contact with a compound which is a substrate for the NEP II polypeptide, obtained according to the method of claim 9, or with a compound which is a inhibitor of the metalloprotease activity of NEP II, said substrate compound or said inhibitor compound being labeled; and

- detecting the presence of said substrate compound or of said inhibitor compound, which is an indication of the presence of the NEP II polypeptide.

13. (Previously Presented) The method according to claim 11 further comprising manufacturing a medicinal product from the compounds which are capable of inhibiting the metalloprotease activity of the NEP2 polypeptide.

14. (Cancelled)

15. (Previously Presented) The method of claim 13, wherein said medicinal product is useful for treating disorders involving the peptide transmission in which NEP2 participates.

16. (Previously Presented) The method according to claim 15 wherein said disorder is selected from the group consisting of cardiovascular and neuro-degenerative diseases, growth disorders of endocrine origin, disturbances of the hypothalamo-hypophysial axis and endocrine conditions.